## REMARKS

The application has been amended pursuant to the accompanying Petition under 37 C.F.R. § 1.48(b), to delete Richard Grant Fehon and Christine Marie Blaumueller as co-inventors in this application.

The specification has been amended to update the status of certain priority applications.

Upon entry of this paper, claims 34, 91-100, 106, 109-110 and 115-116 will be pending and under consideration. Claims 101-105, 108, 111, 113, 114 and 116 have been withdrawn from consideration due to a species election. Claims 90, 107 and 112 have been canceled without prejudice herein. Claims 34, 94, 95, 96, 104, 106, 108 and 111 are amended herein for purposes of clarity. Claim 34 has been amended to specify administering to a mammal, as supported in the specification at page 26, lines 22-23. Claims 34 and 96 have been amended to specify a mammalian Notch protein, as supported in the specification at page 26, lines 22-23 and page 47, line 8. Claim 34 has also been amended to specify the disease or disorder as a malignancy characterized by increased Notch activity or increased expression of a Notch protein or of a Notch derivative capable of being bound by an anti-Notch antibody, relative to said Notch activity or expression in an analogous non-malignant sample, as supported in the specification, *inter alia*, at page 17, lines 25-30 and page 20, lines 15-23. Claims 94 and 95 have been amended to change their claim dependencies in view of the cancellation of claim 90. Claims 104, 106, 108 and 111 have been amended to replace the term "a toporythmic protein" with "a Delta protein or Serrate protein". Support for the amendments to claims 104, 106, 108 and 111 is found in the specification at page 5, lines 25-31 and at page 12, line 27 to page 13, line 2.

No new matter is added.

### 1. The Information Disclosure Statement

The Examiner has stated that the Information Disclosure Statement filed on January 24, 2005 fails to comply with 37 C.F.R. § 1.98(a)(2), since copies of certain cited references were not provided. In response, Applicants respectfully note that the Examiner's assertion that the Information Disclosure Statement filed on January 24, 2005 was not in compliance with 37 C.F.R. § 1.98(a)(2) is erroneous. According to 37 C.F.R. § 1.98(d), a copy of any patent, publication, pending U.S. application or other information, as specified in 37 C.F.R. § 1.98(a) is required to be provided even if previously submitted to, or cited by, the Patent Office in an

earlier application, unless the earlier application is properly identified in the information disclosure statement and is relied on for an earlier effective filing date under 35 U.S.C. § 120 and the information disclosure statement submitted in the earlier application complies with 37 C.F.R. § 1.98(a)-(c).

In the present case, all of the cited references were submitted to, or cited by, the Patent Office in earlier applications, which applications are relied upon for an earlier effective filing date under 35 U.S.C. § 120 and which applications were properly identified in the Information Disclosure Statement filed on January 24, 2005. Further, each of the information disclosure statements filed in the earlier applications complied with 37 C.F.R. § 1.98(a)-(c).

Nevertheless, since these references could not be located by the Examiner, Applicants provide herewith a copy of each of the references that could not be located in the parent application files: References C02-C04, C06-C14, C16-C19, and C21-C76.

**2. The Specification**

The Examiner has required that an updated status of parent patent applications be included in the first sentence of the specification. In response, Applicants have amended the specification on page 1 to note that patent applications 09/546,504 filed May 4, 2002, 07/955,012 filed September 30, 1992 and 07/879,038 filed April 30, 1992 are now abandoned.

**3. The Rejection under 35 U.S.C. § 112, Second Paragraph, Is In Error**

Claims 34, 90-100, 106, 107, 109-110 and 115 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. In particular, the Examiner alleges that the term "Notch activity" in claim 90 and the term "function of a Notch protein" in claim 34 are relative terms which render the claims indefinite.

Applicants respectfully disagree with the Examiner's allegations. The "distinctly claim" requirement of 35 U.S.C. § 112, second paragraph, means that the claims must have a clear and definite meaning when construed in light of the complete patent document. *Standard Oil Co. v. American Cyanamide Co.*, 774 F.2d 448, 227 U.S.P.Q. 293 (Fed. Cir. 1985). The test of definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.* 806 F.2d 1565,

1 U.S.P.Q.2d 1081 (Fed. Cir. 1986). A claim need not describe the invention, such description being provided by the specification's disclosure section. *Id.*

Applicants respectfully submit that the terms "Notch activity" and "function of a Notch protein" would be clearly understood by those of skill in the art. As described in the background section of the present application at pages 1-3, and as known to those of skill in the art, Notch is a transmembrane protein which is involved in a signaling pathway transducing extracellular signaling events (*e.g.*, binding of Delta to the extracellular domain) to the nucleus, which results in the alteration of gene transcription (*e.g.*, activation of basic helix-loop-helix (bHLH) genes in the Enhancer of Split complex). Further, the Examiner's attention is invited to the specification at page 16, lines 24-29 which states that:

> Notch functions as a receptor whose extracellular domain mediates ligand-binding, resulting in the transmission of developmental signals by the cytoplasmic domain. The phenotypes observed also suggested that the cdc10/ankyrin repeat region within the intracellular domain plays an essential role in Notch mediated signal transduction events (intracellular function).

Accordingly, function of a Notch protein or Notch activity is understood as a function of the Notch protein or an activity of the Notch protein within this signal transduction pathway. Such functions include, but are not limited to, directly binding to Delta or Serrate, see, *e.g.*, Sections 6-8 of the present specification. Moreover, each of these functions can be measured using methods well known in the art such that the antagonizing of the function of a Notch protein or Notch activity can readily be measured. Additionally, measuring the binding of Notch to Delta using cell aggregation assays, and immunoassays, are taught in the present specification. Accordingly, Applicants respectfully submit that the terms "function of a Notch protein" and "Notch activity" would be clearly understood by those of skill in the art, and thus, the withdrawal of this Section 112, second paragraph, rejection is respectfully requested.

**4. The Rejections under 35 U.S.C. § 112, First Paragraph, Are In Error**

**A.** Claims 34, 90-100, 106-107, 109-110 and 115 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, allegedly, does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims. According to the Examiner, the specification, while being enabling for a method of reducing tumor growth in mice, using an antibody to laminin A chain, comprising EGF-like repeats homologous to Notch sequence, does not reasonably provide enablement for a method of treating any disease such as malignancy in

humans, by administering an antibody or a portion of the antibody to any Notch protein or its derivative. The Examiner further contends that the specification does not enable the treatment of any disease comprising the administration of an antibody to any toporythmic protein.

Applicants respectfully disagree with the Examiner and submit that the full scope of the presently pending claims, as amended herein, can be practiced by one skilled in the art without undue experimentation, and thus, the presently pending claims meet all the requirements set forth under 35 U.S.C. § 112, first paragraph.

Preliminarily, Applicants point out that claim 34 has been amended to recite a method of treating a disease or disorder in a mammal comprising administering to a mammal in need of such treatment a therapeutically effective amount of a molecule which antagonizes the function of a mammalian Notch protein, in which the disease or disorder is a malignancy characterized by increased Notch activity or increased expression of a Notch protein or of a Notch derivative capable of being bound by an anti-Notch antibody, relative to said Notch activity or expression in an analogous non-malignant sample. Additionally, Applicants note the pending claims are not directed to administering any molecule that antagonizes the function or activity of any toporythmic protein, contrary to the Examiner's contention in paragraph 18[1] of the Office Action mailed August 9, 2007. The pending claims as amended herein are clearly directed to administering a molecule that antagonizes the function of a mammalian Notch protein.

Under 35 U.S.C. § 112, a patent applicant's specification which contains a teaching of how to make and use the invention must be taken as enabling unless the Patent and Trademark Office provides sufficient reason to doubt the accuracy of the disclosure. *In re Marzocchi*, 439 F.2d 220, 223 24, 169 U.S.P.Q. 367, 369 70 (CCPA 1971). The claimed invention disclosed in the specification cannot be questioned on the unsupported skepticism of the Examiner. *Ex parte Linn*, 123 U.S.P.Q. 262 (PTO Bd. Pt. App. Int. 1959); *Ex parte Rosenwald*, 123 U.S.P.Q. 261 (PTO Bd. Pt. App. Int. 1959) (emphasis added). The number and variety of examples is irrelevant if the disclosure is "enabling" and set forth the "best mode contemplated." There is no absolute statutory requirement for a working example if the disclosure is such that one skilled in the art can practice the claimed invention. *In re Borkowski et al.*, 164 U.S.P.Q. 642 (CCPA 1970) (emphasis added). Even in an unpredictable art, Section 112 does not require disclosure of a test of every species encompassed by the claims. *In re Angstadt*, 190 U.S.P.Q. 214, 218 (CCPA 1976). An invention is enabled even though the disclosure may require some routine

[1] Applicants respectfully submit that they do not understand the underscored sentence in paragraph 18 of the Office Action since the Examiner has not indicated how the Notch derivatives or fragments have been interpreted by the Examiner. Applicants respectfully request clarification.

experimentation to practice the invention. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). The fact that the required experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985). A considerable amount of experimentation is permitted if it is merely routine or the specification provides a reasonable amount of guidance and direction to the experimentation. *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988); *In re Jackson*, 217 USPQ 804, 807 (PTO Bd. Pt. App. Int. 1982) (emphasis added). Finally, the Examiner has the burden of showing that the disclosure entails undue experimentation. *In re Angstadt*, 537 F.2d 498, 190 U.S.P.Q. 214 (CCPA 1976) (emphasis added).

Applicants respectfully submit that the Examiner has not shown that one skilled in the art would have had to engage in undue experimentation in order to practice the claimed invention. The Examiner does not explain why the disclosed embodiments of treating diseases or disorders with a molecule that antagonizes the function of a Notch protein do not adequately support treating a malignancy by administering to a subject a therapeutically effective amount of a molecule that antagonizes the function of a Notch protein. An invention is enabled when the amount of experimentation required to practice the invention is routine and the specification provides a reasonable amount of guidance and direction to the experimentation.

Applicants submit that the specification provides considerable guidance and direction to practice the claimed invention without undue experimentation. The Examiner's attention is invited to the specification at page 4, lines 18-31 which states:

> The present invention relates to therapeutic and diagnostic methods and compositions based on Notch proteins and nucleic acids. The invention provides for treatment of disorders of cell fate or differentiation by administration of a therapeutic compound of the invention. Such therapeutic compounds (termed herein "Therapeutics") include: Notch proteins and analogs and derivatives (including fragments) thereof; antibodies thereto; nucleic acids encoding the Notch proteins, analogs, or derivatives; Notch antisense nucleic acids; as well as toporythmic proteins and derivatives which bind to or otherwise interact with Notch proteins, and their encoding nucleic acids and antibodies. In a preferred embodiment, a Therapeutic of the invention is administered to treat a cancerous condition, or to prevent progression from a pre-neoplastic or non-malignant state into a neoplastic or a malignant state.

The specification continues on page 5 disclosing that Therapeutics which antagonize, or inhibit, Notch function (hereinafter "Antagonist Therapeutics") are administered for therapeutic

effect, and such Antagonist Therapeutics include but are not limited to neutralizing anti-Notch antibodies.

Further, the specification describes in detail in Sections 5.1 and 5.2 therapeutic and prophylactic uses for Antagonist Therapeutics. The Examiner's attention is invited to the specification, which states:

> As stated supra, the Antagonist Therapeutics of the invention are those Therapeutics which antagonize, or inhibit, a Notch function. Such Antagonist Therapeutics are most preferably identified by use of known convenient in vitro assays, *e.g.*, based on their ability to inhibit binding of Notch to other proteins (see Sections 6-8 herein), or inhibit any known Notch function as assayed in vitro, although genetic assays (e.g., in Drosophila) may also be employed. In a preferred embodiment, the Antagonist Therapeutic is a protein or derivative thereof comprising a functionally active fragment such as an adhesive fragment of Notch. In specific embodiments, such an Antagonist Therapeutic may be those adhesive proteins encoded by the appropriate constructs described in Sections 6 and 7 infra, or proteins comprising the Notch extracellular region, in particular ELR 11 and ELR 12, or an antibody thereto, or an analog/competitive inhibitor of a Notch intracellular signal-transducing region, a nucleic acid capable of expressing a Notch adhesive fragment, or a Notch antisense nucleic acid (see Section 5.5 herein).[2]
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> In another embodiment, a Therapeutic is indicated for use which exhibits the desired effect, inhibition or promotion of cell growth, upon a patient cell sample from tissue having or suspected of having a hyper- or hypoproliferative disorder, respectively. Such hyper- or hypoproliferative disorders include but are not limited to those described in Sections 5.1.1 through 5.1.3 infra.[3]
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> The Antagonist Therapeutics are administered therapeutically (including prophylactically): (1) in diseases or disorders involving increased (relative to normal, or desired) levels of Notch function, for example, where the Notch protein is overexpressed or overactive; and (2) in diseases or disorders wherein in vitro (or in vivo) assays indicate the utility of Notch antagonist administration. The increased levels of Notch function can be readily detected by methods such as those described above, by quantifying protein and/or RNA. In vitro assays with cells of patient tissue sample or the appropriate cell line or cell type, to determine therapeutic utility, can be carried out as described above.[4]
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[2] Specification, page 13, line 19 to page 14, line 2
[3] Specification, page 16, lines 1-6
[4] Specification, page 17, line 25 to page 18, line 2

> Malignant and pre-neoplastic conditions which can be tested as described supra for efficacy of intervention with Antagonist or Agonist Therapeutics, and which can be treated upon thus observing an indication of therapeutic utility, include but are not limited to those described below in Sections 5.1.1 and 5.2.1.[5]
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> The Therapeutics of the invention can be administered to prevent progression to a neoplastic or malignant state, including but not limited to those disorders listed in Table 1. Such administration is indicated where the Therapeutic is shown in assays, as described supra, to have utility for treatment or prevention of such disorder. Such prophylactic use is indicated in conditions known or suspected of preceding progression to neoplasia or cancer, in particular, where non-neoplastic cell growth consisting of hyperplasia, metaplasia, or most particularly, dysplasia has occurred (for review of such abnormal growth conditions, see Robbins and Angell, 1976, Basic Pathology, 2d Ed., W.B. Saunders Co., Philadelphia, pp. 68 79.)[6]
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> In another specific embodiment, an Antagonist Therapeutic of the invention is administered to a human patient to prevent progression to breast, colon, or cervical cancer.[7]

The specification also describes in detail in Section 5.4 on pages 26-30 delivery systems and modes of administration of a Therapeutic of the present invention. The specification in Section 5.4 further teaches pharmaceutical compositions comprising a Therapeutic of the invention, and a pharmaceutically acceptable carrier. Furthermore, the specification in Section 5.4 teaches that determining appropriate dosages is a matter of routine optimization that can be carried out by using standard assays in the art.

Moreover, there is sound scientific reasoning that there is a molecular basis for the use of an antagonist of Notch function, *e.g.*, an anti-Notch antibody, as a cancer therapeutic. The Examiner's attention is invited to Section 10.1 in the specification wherein it is demonstrated that in all of the tumors examined (human breast, colon and cervical cancer) Notch was expressed at a higher level than in the corresponding non-cancerous tissue. The Examiner's attention is also invited to Ellisen *et al.*, 1991, Cell 66:649-661 (Ref. C20, of record) ("Ellisen"). Ellisen demonstrates that in three separate cases of human T cell lymphoblastic leukemia ("T-ALL") a chromosomal translocation involving human Notch is involved, which leads to expression of a truncated Notch product lacking most of the extracellular domain. Such

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[5] Specification, page 18, lines 5-9
[6] Specification, page 23, line 30 to page 24, line 8
[7] Specification, page 25, lines 26-28

truncated Notch products are taught in the specification of the instant application at page 16, lines 21-22 to be dominant activated gene products, *i.e.*, constitutively active gene products.

Further, Applicants submit herewith additional evidence showing the role of Notch in malignancies and evidence supporting that Notch antagonists can be used to treat malignancies. The Examiner's attention is invited to the following publications, discussed in detail below[8]:

Li *et al.*, 2008, J. Biol. Chem., in press ("Li"), (Ref. C103, made of record in the Third Supplemental Information Disclosure Statement submitted herewith);

Kogoshi *et al.*, 2007, Oncology Reports 18:77-80 ("Kogoshi"). (Ref. C104, made of record in the Third Supplemental Information Disclosure Statement submitted herewith);

Park *et al.*, 2006, Cancer Res. 66:6312-6318 ("Park"), (Ref. C105, made of record in the Third Supplemental Information Disclosure Statement submitted herewith);

Konishi *et al.*, 2007, Cancer Res. 67:8051-8057 ("Konishi"), (Ref. C106, made of record in the Third Supplemental Information Disclosure Statement submitted herewith);

Krop *et al.*, 2006, Abstract 6097, Breast Cancer Research and Treatment 100:Supplement 1 ("Krop"). (Ref. C107, made of record in the Third Supplemental Information Disclosure Statement submitted herewith);

Farnie *et al.*, 2007, Stem Cell Rev. 3:169-175 ("Farnie I"), (Ref. C108, made of record in the Third Supplemental Information Disclosure Statement submitted herewith);

Farnie *et al.*, 2007, J. Natl. Cancer Inst. 99:616-627 ("Farnie II"), (Ref. C109, made of record in the Third Supplemental Information Disclosure Statement submitted herewith);

Dontu *et al.*, 2004, Cancer Res. 6:R605-R615 ("Dontu"), (Reference C110, made of record in the Third Supplemental Information Disclosure Statement submitted herewith);

Politi *et al.*, 2004, Sem. Cancer Biol. 14:341-347 ("Politi") (Reference C111, made of record in the Third Supplemental Information Disclosure Statement submitted herewith);

Reedijk *et al.*, 2005, Cancer Res. 65(18):8530-8537 ("Reedijk") (Reference C112, made of record in the Third Supplemental Information Disclosure Statement submitted herewith);

Büchler *et al.*, 2005, Ann. Surg. 242:791-801 ("Büchler") (Reference C113, made of record in the Third Supplemental Information Disclosure Statement submitted herewith);

[8] Applicants note that post filing date references can be used to address the accuracy of a statement made in the specification, *i.e.*, that a malignancy can be treated by antagonizing the function of a Notch protein. *See Application of Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A., 1971), fn. 4.

Nam *et al.*, 2002, Curr. Opin. Chem. Biol. 6:501-509 ("Nam") (Reference C114, made of record in the Third Supplemental Information Disclosure Statement submitted herewith);

Jundt *et al.*, 2002, Blood 99(9):3398-3404 ("Jundt") (Reference C115, made of record in the Third Supplemental Information Disclosure Statement submitted herewith);

Miele *et al.*, 2006, Curr. Cancer Drug Targets 6:313-323 ("Miele") (Reference C116, made of record in the Third Supplemental Information Disclosure Statement submitted herewith);

Jang *et al.*, 2000, Curr. Opin. Mol. Therapeutics 2(1):55-65 ("Jang") (Reference C117, made of record in the Third Supplemental Information Disclosure Statement submitted herewith);

Purow *et al.*, 2005, Cancer Res. 65(6):2353-2363 (Ref. C88, of record);

Veeraraghavalu *et al.*, 2004, J. Virology 78:8687-8700 (Ref. C93, of record);

Kiaris *et al.*, 2004, Am. J. Pathology 165:695-705 (Ref. C81, of record);

Hoek *et al.*, 2004, Cancer Research 64:5270-5282 (Ref. C80, of record);

Hayashi *et al.*, 2004, Tumor Biology 25:99-105 (Ref. C78, of record);

Dang *et al.*, 2003, Oncogene 22:1988-1997 (Ref. C77, of record);

Patel *et al.*, 2005, Cancer Res. 65(19):8690-8697 (Ref. C85, of record);

Santagata *et al.*, 2004, Cancer Res. 64:6854-6857 (Ref. C90, of record);

Harper *et al.*, 2002, Clin. Genet. 64:461-472 (Ref. C79, of record).

Li discloses the development of monoclonal antibodies (A4 and A8) against Notch3, which are able to inhibit the activation of Notch3 by multiple DSL ligands, including cell-associated Jagged1, Jagged2, Dll1 and soluble Dll4, and Jagged 1 adsorbed to the surface of culture dishes. Further, these antibodies also inhibited Jagged 1-induced up-regulation of *HES5* and *HEY2*, two well-characterized Notch pathway genes (paragraph bridging pages 4-5). Applicants submit that such data clearly shows that anti-Notch antibodies are capable of acting as antagonists of Notch function.

Kogoshi teaches that Notch signaling is involved in the growth of various hematological malignancies and that about half of acute T-lymphoblastic leukemia cases have activating Notch mutations (paragraph bridging the left and right columns on page 77). Kogoshi also teaches that γ-secretase inhibitors block Notch activation and can suppress the growth of acute T-

lymphoblastic leukemia (T-ALL) cells with Notch 1 mutations, as well as some types of B-ML and AML cells, and that clinical trials of a γ-secretase inhibitor have begun in the United States for refractory T-ALL (see Abstract, page 77, right column and page 80, right column).

Park discloses that a human Notch gene, Notch3, was the gene that showed the most significant amplification in amplified ovarian serious carcinomas, and that inactivation of Notch3 by both γ-secretase inhibitor and Notch3-specific small interfering RNA suppressed cell proliferation and induced apoptosis in cell lines that overexpressed Notch3 but not in those with minimal amount of Notch3 expression. Park states that the results indicate that Notch3 is required for proliferation and survival of Notch3-amplified tumors and that inactivation of Notch3 can be a potential therapeutic approach for ovarian carcinomas (Abstract). Park concludes on page 6317, right column that "[o]ur findings suggest that Notch3 amplification may play an important role in the development of ovarian carcinomas; moreover, these findings provide a rationale for future development of Notch3-based therapy for ovarian cancer."

Konishi demonstrated that a high percentage of lung cancer cell lines expressed Jagged1, Notch receptors, and their transcriptional target genes, suggesting that the Notch pathway plays an important role in lung cancer biology (Abstract). Konishi further discloses that the γ-secretase inhibitor (MRK-003) inhibited Notch signaling, inhibited serum independence, and, *in vitro* and *in vivo*, reduced tumor cell growth and induced apoptosis in lung cancer cells (Abstract). Konishi states in the Abstract that "inhibition of Notch receptor activation represents a compelling treatment strategy."

Krop presents data from a phase I pharmacokinetic and pharmacodynamic trial of the novel oral Notch inhibitor MK-0752 in patients with advanced breast cancer and other solid tumors. Krop reports that a significant decrease in Notch intracellular domain expression was observed in post-treatment tissue biopsies, indicating that Notch function was being inhibited.

Farnie I discloses that Notch signaling is highly activated in ductal carcinoma in situ (DCIS), a pre-invasive breast lesion, compared to normal breast and that inhibition of Notch using a γ-secretase inhibitor or a Notch 4 neutralizing antibody reduced DCIS mammosphere forming efficiency (MFE) (page 173, right column), indicating that "Notch signaling and other stem cell self-renewal pathways may represent novel therapeutic targets to prevent recurrence of pre-invasive and invasive breast cancer" (page 169, right column). Farnie I also discloses that that aberrant activation of Notch signaling is an early event in breast cancer and that high expression of Notch1 intracellular domain in DCIS also predicted a reduced time to recurrence 5 years after surgery (see Abstract). On page 173, right column, Farnie I states that their results

suggest that targeting both of these pathways (anti-Notch antibody and γ-secretase inhibitor) may have therapeutic value for DCIS.

Farnie II discloses that ductal carcinoma in situ (DCIS) is a noninvasive breast malignancy that, if untreated, progresses to invasive cancer in 30% to 50% of patients (page 616, left column), and that treatment of DCIS tissue samples with the γ-secretase inhibitor DAPT or with Notch 4 neutralizing antibody reduced DCIS mammosphere forming efficiency, suggesting that the Notch receptor signaling pathway is directly involved in the regulation of DCIS mammosphere formation and/or growth (page 624, right column). Farnie II states on page 626, left column that the data strongly suggest that targeting the Notch pathway would be therapeutically useful in treating DCIS.

Dontu discloses that mammospheres, when grown in a three-dimensional culture system, develop extensive ductal lobuloalveolar structures similar in morphology to those found *in vivo* (see page R611, right column). When such mammosphere three-dimensional cultures were exposed to an inhibitor of Notch function, *i.e.*, a γ-secretase inhibitor or an anti-Notch antibody, the branching morphogenesis was completely inhibited (page R611, right column). Dontu explains that the results presented suggest that Notch signaling plays a critical role in normal human mammary development and that abnormal Notch signaling may contribute to mammary carcinogenesis by deregulating the self-renewal of normal mammary stem cells (Abstract).

Politi is a review article concerning Notch in mammary gland development and breast cancer which reviews studies of mammary tumorigenesis induced in mouse and *in vitro* culture models providing evidence that Notch activation is a causal factor in human breast cancer (Abstract).

Reedijk discloses that human patients with breast tumors expressing high levels of Jagged or Notch had a significantly poorer overall survival compared to patients expressing low levels of these genes (Abstract). Reedijk states that "[t]hese data (a) identify novel prognostic markers for breast cancer, (b) suggest a mechanism whereby Notch is activated in aggressive breast tumors, and (c) may identify a signaling pathway activated in poor prognosis breast cancer which can be therapeutically targeted" (Abstract). Thus, Reedijk suggests that the Notch signaling pathway can be targeted as a means to treat breast cancer (Abstract).

Büchler discloses that expression of Notch3, Notch4, and Notch ligands Jagged1, Jagged2 and Delta1 was upregulated in pancreatic cancer samples as compared to normal pancreatic tissue (Abstract, and page 794, left column to page 795, left column). Büchler concludes that "[t]he Notch pathway most likely regulates neurovascular development in

pancreatic cancer. Activation of this signaling pathway by constitutive Notch-1 mutants and by Jagged-1 causes an angiogenic and invasive tumor phenotype. Specific blockade of Notch signaling may therefore be beneficial for patients with pancreatic cancer" (Abstract).

Nam is a review article describing the role of Notch in human diseases and that the manipulation of Notch signaling may be useful for therapeutic purposes in the treatment of cancer and in stem cell maintenance (Abstract, and page 501, right column to page 502, left column and page 504, right column to page 505, right column).

Jundt shows that Notch1 is strongly expressed in B-cell-derived HRS cells and in tumor cells of T-cell-derived anaplastic large cell lymphoma (ALCL) suggesting that activated Notch1 signaling plays an important role in the pathobiology of Hodgkin disease and ALCL, and suggests that pharmacologic manipulation of the Notch1 system might have therapeutic potential in these lymphomas (Abstract and page 3398, right column).

Miele is a review article that summarizes the evidence linking Notch signaling to several types of cancer (Abstract). Miele on pages 316-317 discusses the potential of Notch inhibitors as cancer therapeutics, as well as discusses a number of strategies to achieve inhibition of Notch signaling, including antisense Notch and anti-Notch antibodies.

Jang is a review article discussing Notch and its role in regulating cell differentiation, proliferation and apoptosis in many cells, including neoplastic cells and discusses, *inter alia,* the role of Notch signaling in cancer cells and strategies through which Notch-targeting biologicals may be used to increase the effectiveness of multimodality cancer treatment, including cancer vaccines (Abstract). Further, Jang on pages 60-61 discusses the possible use of Notch antagonists, including antisense constructs, antibodies, and a peptide consisting of EGF-like repeats 11 and 12, to treat cancer.

Purow shows over-expression of Notch and its ligands Delta and Jagged (a Serrate homolog) in many glioma cell lines and primary human gliomas. Further, down-regulation of Notch, Delta or Jagged (Serrate) induces apoptosis and inhibits proliferation of multiple glioma cell lines (see Abstract.) Additionally, Purow shows that pre-treatment of glioma cells with the antagonists of Notch function, Notch-1 siRNA or Delta-like-1 siRNA, significantly prolonged survival of mice implanted intracranially with the glioma cells as compared to mice implanted with control glioma cells (see page 2360, right column to page 2361, left column and Figures 4F and 5C).

According to Veeraraghavalu, inhibiting Notch signaling inhibited the tumorigenicity of a transformed cell line in nude mice, which cell line was previously shown to be susceptible to growth inhibition by inhibiting Notch expression (Abstract). Veerarghavalu on page 8698, left column, explains that by inhibiting Notch signaling function by expressing soluble Jagged1, Manic Fringe and siRNA against Jagged1 the tumorigenicity of CaSki cells *in vivo* could be blocked, which is consistent with a role for Notch signaling in maintaining the neoplastic phenotype.

Kiaris demonstrates that expression of a constitutively-active form of Notch1 in mammary epithelium induces the rapid development of pregnancy/lactation-dependent neoplasms. Kiaris also demonstrates that the Notch antagonist Deltex can inhibit human-ras1-driven, cyclin D1-dependent mammary oncogenesis in cells expressing endogenous levels of Notch.

Hoek describes a study assessing differential gene expression between melanoma cells and normal human melanocytes. Hoek shows that, *inter alia*, Notch expression is up-regulated in melanoma cells as compared to normal melanocytes and states that Notch plays a role in early transformation – see Hoek at page 5278, left column. Further, Hoek discloses that increased Notch2 expression has also been detected in two advanced primary melanoma tumors as compared with benign nevi.

Hayashi discloses that Notch 1 and the Notch ligand Jagged 2 (Serrate) are normally expressed in non-cancerous testicular tissues but that their expression is absent in seminomas, thus playing a role in the cell fate or differentiation of testicular tissue. On page 104, right column, Hayashi explains that there is increasing evidence that the Notch signaling network regulates cell differentiation, proliferation and apoptosis in many cells, including mammalian germ cells and neoplastic cells of human malignancies, which suggests the possibility that genetic or pharmacological manipulation of Notch signaling is a novel potential strategy for human neoplasms, including testicular tumors.

Dang discloses that ectopic expression of Notch3 in airway epithelium potentially contributes to the multi-step evolution of lung cancer through the inhibition of terminal differentiation.

Patel shows that the Notch ligand Delta is involved in angiogenesis and that expression of Delta is up-regulated in the vasculature of renal cell carcinoma as compared to normal kidney. Patel concludes that modulation of Delta may represent a novel anti-angiogenic therapy (see Abstract).

Santagata shows that the Notch ligand Jagged (a Serrate homolog) is more highly expressed in metastatic prostate cancer as compared to localized prostate cancer or benign prostatic tissues (see Abstract). Santagata also shows on page 6857, left column, that differential expression of Jagged is observed in a number of other cancers, including squamous cell lung cancer and carcinoid tumors. Further, there was a trend toward differential Jagged expression in fibroadenomas, pilocytic astrocytoma and atypical teratoid/rhabdoid tumors.

Harper is a review article which summarizes much of the knowledge of the Notch pathway with regard to its role in cell fate or differentiation and its role in cancers and other pathologies in humans. In particular, Harper discusses on pages 467 and 468 three different diseases other than malignancies that are caused by mutations in the Notch pathway. Alagille syndrome, discussed above, and spondylocostal dysostosis are two developmental disorders due to mutations in Serrate and Delta, respectively, which are each believed to be due to a loss of Notch function. Another disease, CADASIL, is associated with mutations in Notch3, which results in systemic arteriopathy leading to strokes, mood disorders, migraine and progressive dementia.

The foregoing evidence shows that activation of Notch function is associated with malignancy. Regarding antibodies, it was well known to those of skill in the art well prior to the effective filing date of the present application that antibodies to a protein can often routinely be obtained that will bind to the protein and disrupt its activity. Therefore, based on the teaching of the present specification regarding Notch and malignancy, as well as the disclosure for producing anti-Notch antibodies, and the common knowledge in the art regarding antibodies, one skilled in the art would clearly understand the molecular basis for the use of an anti-Notch antibody as a therapeutic for treating malignancy.

An invention meets the standard for successful practice set by Section 112 unless the invention is "totally incapable of achieving a useful result." *Brooktree v. Advances Micro Devices*, 24 U.S.P.Q.2d 1401, 1412 (Fed. Cir. 1992). The Examiner's attention is directed to the opinion of the Court of Appeals for the Federal Circuit (Federal Circuit) in *In re Brana*, 34 U.S.P.Q.2d 1437 (Fed. Cir. 1995). In *Brana*, the Board had affirmed a final rejection under Section 112, 1st paragraph, of claims covering certain compounds asserted to be useful as anti-tumor substances because it was alleged that the specification was non-enabling since it did not sufficiently establish that the claimed compounds had a practical utility, *i.e.*, as anti-tumor agents. 34 U.S.P.Q.2d at 1439. The Federal Circuit emphatically reversed the Board's decision. The Federal Circuit explained the legal standard for compliance with the relevant Section 112

requirement, explaining that "unless there is reason to doubt the objective truth of the statements contained [in the specification] which must be relied on for enabling support", a specification's disclosure "must be taken as in compliance with the enabling requirement." *Id.* at 1441 (emphasis in the original). Further, the *Brana* Court made clear that the Patent and Trademark Office has the initial burden of challenging a presumptively correct assertion of utility; evidence must be presented that those of skill in the art would doubt the disclosure. Only then must the applicant provide rebuttal evidence. Further, the Federal Circuit in *Brana* explained that even if one of skill in the art would have questioned the asserted utility, all applicants need do to overcome the rejection is to proffer sufficient evidence to convince one skilled in the art of the asserted utility. *Id.* at 1441. In the present invention, Applicants have provided such evidence showing, *inter alia*, that antagonizing the function of a Notch protein has therapeutic value in an animal model (see Konishi, Purow, Veeraraghavalu and Kiaris).

The foregoing evidence reasonably correlates with Applicants' asserted use of the invention, *i.e.*, that antagonists of Notch function (*e.g.*, neutralizing antibodies) can be used to treat a malignancy. The claimed invention thus satisfies 35 U.S.C. § 112, first paragraph.

With regard to the Examiner's contention that the art recognized the unpredictability of treating tumors with antibodies in view of Jain, 1994, Scientific American July, pp. 58-85 (Ref. V cited by the Examiner), Applicants note that Jain only deals with solid tumors, whereas Notch signaling is involved in both solid and non-solid tumors, *i.e.*, leukemia (see, *e.g.*, Ellisen *et al.*, 1991, Cell 66:646-661, Ref. C20 of record, which discusses the role of Notch in T-cell leukemia). Applicants point out that there is no absolute statutory requirement for a working example if the disclosure is such that one skilled in the art can practice the claimed invention, *In re Borkowski et al.*, 164 U.S.P.Q. 642 (CCPA 1970) (emphasis added), and that Section 112 does not require the *in vivo* testing of the methods and compositions encompassed by the claims.

In view of the foregoing remarks, it is respectfully submitted that the specification provides sufficient teaching to allow one of skill in the art to successfully practice the claimed invention without undue experimentation. Thus, the rejection of claims 34, 90-100, 106, 107, 109, 110 and 115 under 35 U.S.C. § 112, first paragraph, should be withdrawn.

**B.** Claims 34, 90-100, 106, 107, 109, 110 and 115 are rejected under 35 U.S.C. § 112. first paragraph, allegedly, for containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In

particular, the Examiner alleges that the brief description in the specification describing antibodies to human Notch homologs hN and TAN-1 does not constitute a representative number of species of antibodies to any toporythmic protein, or Notch fragment or Notch derivative to be used for administration in humans for cancer treatment and that only antibodies to hN and TAN-1, but not the full breadth of the claims meets the written description provision of 35 U.S.C. § 112, first paragraph.

Preliminarily, Applicants note that the term "a toporythmic protein" in claims 104, 106, 108 and 111 has been replaced by the term "a Delta protein or Serrate protein."

Applicants respectfully disagree with the Examiner and point out that in order to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, an Applicant "must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Vas-Cath Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). This inquiry is often phrased as whether the patent specification provides "adequate support" for the claim(s) at issue. *Id.* at 1560.

With respect to the antibodies recited in the claims, the case law has made it clear that written description can be satisfied through disclosure of relevant identifying characteristics, *i.e.*, structure, other physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics, such that the inventor is able to define the claimed compound so as to distinguish it from other materials. See, *Amgen, Inc. v. Chugai Pharmaceutical Co., Inc.*, 927 F.2d 1200, 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991); *Fiers v. Revel*, 984 F.2d 1164, 25 U.S.P.Q.2d 1601 (Fed. Cir. 1993).

> [I]t is well established in our law that the conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials and to describe how to obtain it. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its methods of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it.

*Amgen*, at 1206, 1021 (citations omitted).

> If a conception . . . . requires a precise definition, such as by structure, formula, chemical name, or physical properties, as we have held [in Amgen], then a description also requires that degree of specificity. To paraphrase the Board, one cannot describe what one has not conceived.

*Fiers* at 1171, 1606.

Applicants submit that in view of the known functional and structural characteristics of antibodies and fragments thereof, an antibody to a protein meets the written description requirements of Section 112 when the protein is uniquely identified and distinguished from other proteins. Applicants submit Notch, Delta and Serrate proteins are well-defined and uniquely distinguished proteins. Notch proteins, Delta proteins and Serrate proteins are well known in the art (see *e.g.*, the specification at Section 2.1, pages 1-4), and examples of these proteins are described in the present specification. For example, in the present specification two human Notch sequences are set forth (see Figures 10, 11, 13 and 17). Further, the sequences of *Drosophila* and *Xenopus* Notch are depicted in Wharton *et al.*, 1985, Cell 43:567-581 (Ref. C72, of record) and Coffman *et al.*, 1990, Science 249:1438-1441 (Ref. C14, of record), respectively. Further, *Drosophila* Delta and *Drosophila* Serrate sequences are disclosed in Kopczynski *et al.*, 1988, Genes Dev 2:1723-1735 (Ref. C39, of record) and Fleming *et al.*, 1990, Genes Dev 4:2188-2201 (Ref. C23, of record), respectively. Applicants submit that Notch, Delta and Serrate proteins are thus well-characterized in the art and in the specification, so as to be distinguishable from other proteins. Thus, the specification provides an adequate written description of an antibody to a Notch, Delta or Serrate protein.

In the present situation, Applicants submit that the claimed subject matter is described by the specification within the meaning of 35 U.S.C. § 112, first paragraph.

**5. The Rejection under 35 U.S.C. § 102(e) Is In Error**

Claims 34, 96, 106 and 107 are rejected under 35 U.S.C. § 102(e) as, allegedly, anticipated by U.S. Patent No. 5,211,657 to Yamada *et al.* ("Yamada"). According to the Examiner, Yamada teaches antibodies generated to the A chain of laminin that can be used for the treatment of diseases, like cancer, and that laminin A chain has sequence homology with Notch. Further, according to the Examiner, although Yamada does not explicitly teach administration of the antibody to a subject, the limitation is clearly inherent in the reference. The Examiner concludes that because of the method steps disclosed by Yamada meet the limitations of claims 34, 96, 106 and 107, the method described in Yamada anticipates claims 34, 96, 106 and 107.

Applicants disagree and point out that the Examiner has mistakenly characterized the teachings of Yamada. Contrary to the Examiner's assertion, Yamada teaches in column 3, lines 13-14 that an object of the invention is to raise antibodies specific to certain domains of the A chain, which can be used to block cell adhesion, migration, growth, and neurite outgrowth.

These antibodies are raised against the synthetic peptides deduced from the DNA sequence and against fusion proteins containing a segment of the A chain produced by bacteria (see column 3, lines 14-19). Yamada teaches further in column 3, lines 26-30 that an object of the invention provides synthetic peptides from the A chain which have biological activity including promoting cell attachment, growth, migration, differentiation and regulating metastasis of tumor cells. Furthermore, Yamada states that because laminin is a large and antigenic molecule, clinical use of the whole protein may not be feasible and that small synthetic peptides which contain laminin activity will be very useful and have important clinical applications (see Yamada, column 3, lines 33-37). Yamada teaches in Table III in column 18 and in Examples 6 through 11 the synthetic peptides having laminin activity. Thus, contrary to the Examiner, Yamada does not teach antibodies generated against laminin A that can be used in the treatment of diseases, but, rather, Yamada teaches antibodies, generated against the synthetic peptides having biological activity of laminin A that are disclosed in Table III, that can be used in the treatment of diseases.

Applicants have performed BLAST sequence comparisons of the synthetic peptides disclosed in Table III of Yamada with the amino acid sequences of human Notch 1 and Notch 2 proteins, the results of which are attached as Exhibits A and B, respectively. As evidenced by the results of the sequence comparisons, none of the synthetic peptides were found to have any identity or homology with any of the Notch proteins. Thus an antibody generated against one of the synthetic peptides of Yamada would not be expected to cross-react with a mammalian Notch protein. In order for a reference to anticipate a claim, each and every element of the claim must be disclosed in that one reference. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565 (Fed. Cir. 1985). "Anticipation under Section 102 can be found only if a reference shows exactly what is claimed. . ." *Structural Rubber Prod. Co. v. Park Rubber Co.*, 749 F.2d 707 (Fed. Cir. 1984). Since none of the antibodies generated by Yamada would be expected to bind to a mammalian Notch protein, the antibodies of Yamada cannot anticipate an antibody to a mammalian Notch protein, or to a method of using an antibody to a mammalian Notch protein for treating a disease or disorder.

Thus, the Examiner's basis for rejecting claims 34, 96, 106 and 107 under Section 102(e) as anticipated in view of Yamada does not meet the legal standard for anticipation. Thus, Applicants respectfully request that the rejection of claims 34, 96, 106 and 107 under Section 102(e) be withdrawn.

**6. The Rejection under 35 U.S.C. § 103(a) Is In Error**

Claims 95, 97-99, 109 and 110 are rejected under 35 U.S.C. § 103(a) as, allegedly, obvious over U.S. Patent No. 5,211,657 to Yamada *et al.* ("Yamada") in view of Harlow and Lane, 1988, Antibodies: A Laboratory Manual ("Harlow"). According to the Examiner, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the use of antibodies for therapy of Yamada by generating monoclonal antibodies as taught by Harlow.

Applicants respectfully disagree. Yamada, as discussed above, does not teach antibodies to a Notch protein. Harlow merely discloses a method of making monoclonal antibodies. Harlow does not remedy the deficiencies of Yamada and thus, cannot render the claimed methods obvious.

Thus, the Examiner's rejection under Section 103(a) is erroneous and Applicants respectfully request withdrawal of the Section 103(a) rejection of claims 95, 97-99, 109 and 110.

**CONCLUSION**

Applicants respectfully request that the above-made remarks of the present response be entered and made of record in the file history present application.

Applicants request that the Examiner call Adriane M. Antler at (212) 326-3630 if any questions or issues remain.

Respectfully submitted,

by: Helen M. Queen
REG NO 40,207

Date: February 11, 2008

Adriane M. Antler 32,605
Adriane M. Antler (Reg. No.)

**JONES DAY**
222 East 41st Street
New York, New York 10017
(212) 326-3939

Enclosures

# Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

---

**Sequence 1**: gi|24041035|notch 2 preproprotein [Homo sapiens] >gi|143811429|sp|Q04721|NOTC2_HUMAN Neurogenic locus notch homolog protein 2 precursor (Notch 2) (hN2) [Contains: Notch 2 extracellular truncation; Notch 2 intracellular domain] >gi|56205498|emb|CAI18974.1| Notch homolog 2 (Drosophila) [Homo sapiens]
Length = 2471

**Sequence 2**: peptide 1 of claim 1
Length = 16

**No significant similarity was found**

```
CPU time:      0.05 user secs.       0.02 sys. secs          0.07 total secs.
```

# Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

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**Sequence 1**: gi|24041035|notch 2 preproprotein [Homo sapiens] >gi|143811429|sp|Q04721|NOTC2_HUMAN Neurogenic locus notch homolog protein 2 precursor (Notch 2) (hN2) [Contains: Notch 2 extracellular truncation; Notch 2 intracellular domain] >gi|56205498|emb|CAI18974.1| Notch homolog 2 (Drosophila) [Homo sapiens]
Length = 2471

**Sequence 2**: peptide 2 of claim 1
Length = 12

**No significant similarity was found**

```
CPU time:     0.11 user secs.       0.04 sys. secs          0.15 total secs.
```

# Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

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Length = 2471

**Sequence 2**: peptide 3 of claim 1
Length = 11

**No significant similarity was found**

```
CPU time:      0.06 user secs.       0.02 sys. secs          0.08 total secs.
```

# Blast 2 Sequences results



**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

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**Sequence 1**: gi|24041035|notch 2 preproprotein [Homo sapiens] >gi|143811429|sp|Q04721|NOTC2_HUMAN Neurogenic locus notch homolog protein 2 precursor (Notch 2) (hN2) [Contains: Notch 2 extracellular truncation; Notch 2 intracellular domain] >gi|56205498|emb|CAI18974.1| Notch homolog 2 (Drosophila) [Homo sapiens]
Length = 2471

**Sequence 2**: peptide 4 of claim 1
Length = 19

**No significant similarity was found**

```
CPU time:     0.06 user secs.      0.02 sys. secs          0.08 total secs.
```

# Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

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**Sequence 1**: gi|24041035|notch 2 preproprotein [Homo sapiens] >gi|143811429|sp|Q04721|NOTC2_HUMAN Neurogenic locus notch homolog protein 2 precursor (Notch 2) (hN2) [Contains: Notch 2 extracellular truncation; Notch 2 intracellular domain] >gi|56205498|emb|CAI18974.1| Notch homolog 2 (Drosophila) [Homo sapiens]
Length = 2471

**Sequence 2**: peptide 5 of claim 1
Length = 13

**No significant similarity was found**

```
CPU time:     0.06 user secs.      0.02 sys. secs          0.08 total secs.
```

# Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

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**Sequence 1**: gi|24041035|notch 2 preproprotein [Homo sapiens] >gi|143811429|sp|Q04721|NOTC2_HUMAN Neurogenic locus notch homolog protein 2 precursor (Notch 2) (hN2) [Contains: Notch 2 extracellular truncation; Notch 2 intracellular domain] >gi|56205498|emb|CAI18974.1| Notch homolog 2 (Drosophila) [Homo sapiens]
Length = 2471

**Sequence 2**: peptide 6 of claim 1
Length = 10

**No significant similarity was found**

```
CPU time:      0.05 user secs.       0.02 sys. secs          0.07 total secs.
```

# Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

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**Sequence 1**: gi|24041035|notch 2 preproprotein [Homo sapiens] >gi|143811429|sp|Q04721|NOTC2_HUMAN Neurogenic locus notch homolog protein 2 precursor (Notch 2) (hN2) [Contains: Notch 2 extracellular truncation; Notch 2 intracellular domain] >gi|56205498|emb|CAI18974.1| Notch homolog 2 (Drosophila) [Homo sapiens]
Length = 2471

**Sequence 2**: peptide 7 of claim 1
Length = 17

**No significant similarity was found**

```
CPU time:     0.06 user secs.      0.02 sys. secs          0.08 total secs.
```

# Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

---

**Sequence 1**: gi|24041035|notch 2 preproprotein [Homo sapiens] >gi|143811429|sp|Q04721|NOTC2_HUMAN Neurogenic locus notch homolog protein 2 precursor (Notch 2) (hN2) [Contains: Notch 2 extracellular truncation; Notch 2 intracellular domain] >gi|56205498|emb|CAI18974.1| Notch homolog 2 (Drosophila) [Homo sapiens]
Length = 2471

**Sequence 2**: peptide 8 of claim 1
Length = 12

**No significant similarity was found**

```
CPU time:      0.07 user secs.       0.02 sys. secs          0.09 total secs.
```

# Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

---

**Sequence 1**: gi|24041035|notch 2 preproprotein [Homo sapiens] >gi|143811429|sp|Q04721|NOTC2_HUMAN Neurogenic locus notch homolog protein 2 precursor (Notch 2) (hN2) [Contains: Notch 2 extracellular truncation; Notch 2 intracellular domain] >gi|56205498|emb|CAI18974.1| Notch homolog 2 (Drosophila) [Homo sapiens]
Length = 2471

**Sequence 2**: peptide 9 of claim 1
Length = 17

**No significant similarity was found**

```
CPU time:     0.06 user secs.      0.02 sys. secs          0.08 total secs.
```

# Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

---

**Sequence 1**: gi|24041035|notch 2 preproprotein [Homo sapiens] >gi|143811429|sp|Q04721|NOTC2_HUMAN Neurogenic locus notch homolog protein 2 precursor (Notch 2) (hN2) [Contains: Notch 2 extracellular truncation; Notch 2 intracellular domain] >gi|56205498|emb|CAI18974.1| Notch homolog 2 (Drosophila) [Homo sapiens]
Length = 2471

**Sequence 2**: peptide 10 of claim 1
Length = 20

**No significant similarity was found**

```
CPU time:      0.06 user secs.       0.02 sys. secs          0.08 total secs.
```

# Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

---

**Sequence 1**: gi|24041035|notch 2 preproprotein [Homo sapiens] >gi|143811429|sp|Q04721|NOTC2_HUMAN Neurogenic locus notch homolog protein 2 precursor (Notch 2) (hN2) [Contains: Notch 2 extracellular truncation; Notch 2 intracellular domain] >gi|56205498|emb|CAI18974.1| Notch homolog 2 (Drosophila) [Homo sapiens]
Length = 2471

**Sequence 2**: peptide 11 of claim 1
Length = 17

**No significant similarity was found**

```
CPU time:      0.06 user secs.       0.03 sys. secs          0.09 total secs.
```

# Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

---

**Sequence 1**: gi|24041035|notch 2 preproprotein [Homo sapiens] >gi|143811429|sp|Q04721|NOTC2_HUMAN Neurogenic locus notch homolog protein 2 precursor (Notch 2) (hN2) [Contains: Notch 2 extracellular truncation; Notch 2 intracellular domain] >gi|56205498|emb|CAI18974.1| Notch homolog 2 (Drosophila) [Homo sapiens]
Length = 2471

**Sequence 2**: peptide 12 of claim 1
Length = 13

**No significant similarity was found**

CPU time: 0.07 user secs. 0.02 sys. secs 0.09 total secs.

# Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

---

**Sequence 1**: gi|24041035|notch 2 preproprotein [Homo sapiens] >gi|143811429|sp|Q04721|NOTC2_HUMAN Neurogenic locus notch homolog protein 2 precursor (Notch 2) (hN2) [Contains: Notch 2 extracellular truncation; Notch 2 intracellular domain] >gi|56205498|emb|CAI18974.1| Notch homolog 2 (Drosophila) [Homo sapiens]
Length = 2471

**Sequence 2**: peptide 13 of claim 1
Length = 20

**No significant similarity was found**

```
CPU time:     0.07 user secs.      0.02 sys. secs          0.09 total secs.
```

# Blast 2 Sequences results



**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix [BLOSUM62] gap open:[11] gap extension: [1]
x_dropoff: [0] expect:[10.000] wordsize: [3] Filter ☐ View option [Standard]
Masking character option [X for protein, n for nucleotide] Masking color option [Black]
☐ Show CDS translation [Align]

---

**Sequence 1**: gi|148833508|notch1 preproprotein [Homo sapiens] >gi|55961006|emb|CAI13934.1| Notch homolog 1, translocation-associated (Drosophila) [Homo sapiens]
Length = 2555

**Sequence 2**: peptide 1 of claim 1
Length = 16

**No significant similarity was found**

```
CPU time:     0.05 user secs.      0.02 sys. secs          0.07 total secs.
```

# Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.0000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

---

**Sequence 1**: gi|148833508|notch1 preproprotein [Homo sapiens] >gi|55961006|emb|CAI13934.1| Notch homolog 1, translocation-associated (Drosophila) [Homo sapiens]
Length = 2555

**Sequence 2**: peptide 2 of claim 1
Length = 12

**No significant similarity was found**

```
CPU time:      0.06 user secs.       0.03 sys. secs          0.09 total secs.
```

# Blast 2 Sequences results



**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

---

**Sequence 1**: gi|148833508|notch1 preproprotein [Homo sapiens] >gi|55961006|emb|CAI13934.1| Notch homolog 1, translocation-associated (Drosophila) [Homo sapiens]
Length = 2555

**Sequence 2**: peptide 3 of claim 1
Length = 11

**No significant similarity was found**

CPU time: 0.06 user secs. 0.02 sys. secs 0.08 total secs.

# Blast 2 Sequences results



**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

---

**Sequence 1**: gi|148833508|notch1 preproprotein [Homo sapiens] >gi|55961006|emb|CAI13934.1| Notch homolog 1, translocation-associated (Drosophila) [Homo sapiens]
Length = 2555

**Sequence 2**: peptide 4 of claim 1
Length = 19

**No significant similarity was found**

```
CPU time:      0.07 user secs.       0.02 sys. secs          0.09 total secs.
```

# Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

---

**Sequence 1**: gi|148833508|notch1 preproprotein [Homo sapiens] >gi|55961006|emb|CAI13934.1| Notch homolog 1, translocation-associated (Drosophila) [Homo sapiens]
Length = 2555

**Sequence 2**: peptide 5 of claim 1
Length = 13

**No significant similarity was found**

CPU time: 0.06 user secs. 0.02 sys. secs 0.08 total secs.

# Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

---

**Sequence 1**: gi|148833508|notch1 preproprotein [Homo sapiens] >gi|55961006|emb|CAI13934.1| Notch homolog 1, translocation-associated (Drosophila) [Homo sapiens]
Length = 2555

**Sequence 2**: peptide 6 of claim 1
Length = 10

**No significant similarity was found**

```
CPU time:      0.06 user secs.       0.02 sys. secs          0.08 total secs.
```

# Blast 2 Sequences results



**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

---

**Sequence 1**: gi|148833508|notch1 preproprotein [Homo sapiens] >gi|55961006|emb|CAI13934.1| Notch homolog 1, translocation-associated (Drosophila) [Homo sapiens]
Length = 2555

**Sequence 2**: peptide 7 of claim 1
Length = 17

**No significant similarity was found**

```
CPU time:      0.06 user secs.      0.03 sys. secs          0.09 total secs.
```

# Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

---

**Sequence 1**: gi|148833508|notch1 preproprotein [Homo sapiens] >gi|55961006|emb|CAI13934.1| Notch homolog 1, translocation-associated (Drosophila) [Homo sapiens]
Length = 2555

**Sequence 2**: peptide 8 of claim 1
Length = 12

**No significant similarity was found**

```
CPU time:      0.06 user secs.      0.03 sys. secs          0.09 total secs.
```

# Blast 2 Sequences results



**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

---

**Sequence 1**: gi|148833508|notch1 preproprotein [Homo sapiens] >gi|55961006|emb|CAI13934.1| Notch homolog 1, translocation-associated (Drosophila) [Homo sapiens]
Length = 2555

**Sequence 2**: peptide 9 of claim 1
Length = 17

**No significant similarity was found**

CPU time: 0.06 user secs. 0.03 sys. secs 0.09 total secs.

# Blast 2 Sequences results



**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

---

**Sequence 1**: gi|148833508|notch1 preproprotein [Homo sapiens] >gi|55961006|emb|CAI13934.1| Notch homolog 1, translocation-associated (Drosophila) [Homo sapiens]
Length = 2555

**Sequence 2**: peptide 10 of claim 1
Length = 20

**No significant similarity was found**

```
CPU time:      0.07 user secs.       0.03 sys. secs          0.10 total secs.
```

# Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

---

**Sequence 1**: gi|148833508|notch1 preproprotein [Homo sapiens] >gi|55961006|emb|CAI13934.1| Notch homolog 1, translocation-associated (Drosophila) [Homo sapiens]
Length = 2555

**Sequence 2**: peptide 11 of claim 1
Length = 17

**No significant similarity was found**

```
CPU time:      0.07 user secs.       0.03 sys. secs          0.10 total secs.
```

# Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

---

**Sequence 1**: gi|148833508|notch1 preproprotein [Homo sapiens] >gi|55961006|emb|CAI13934.1| Notch homolog 1, translocation-associated (Drosophila) [Homo sapiens]
Length = 2555

**Sequence 2**: peptide 12 of claim 1
Length = 13

**No significant similarity was found**

CPU time: 0.06 user secs. 0.03 sys. secs 0.09 total secs.

# Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

**BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]**

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 0 expect: 10.000( wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

---

**Sequence 1**: gi|148833508|notch1 preproprotein [Homo sapiens] >gi|55961006|emb|CAI13934.1| Notch homolog 1, translocation-associated (Drosophila) [Homo sapiens]
Length = 2555

**Sequence 2**: peptide 13 of claim 1
Length = 20

**No significant similarity was found**

```
CPU time:      0.07 user secs.      0.02 sys. secs          0.09 total secs.
```